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(12) **United States Patent**  
**Morin et al.**(10) **Patent No.:** **US 11,248,031 B2**(45) **Date of Patent:** **\*Feb. 15, 2022**(54) **METHODS OF TREATING DISEASES  
ASSOCIATED WITH FIBROSIS USING  
MODIFIED FGF-21 POLYPEPTIDES**(71) Applicant: **BRISTOL-MYERS SQUIBB  
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COMPANY**, Princeton, NJ (US)( \* ) Notice: Subject to any disclaimer, the term of this  
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U.S.C. 154(b) by 173 days.This patent is subject to a terminal dis-  
claimer.(21) Appl. No.: **16/455,990**(22) Filed: **Jun. 28, 2019**(65) **Prior Publication Data**

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continuation of application No. 14/921,796, filed on  
Oct. 23, 2015, now Pat. No. 9,434,778.(60) Provisional application No. 62/141,383, filed on Apr.  
1, 2015, provisional application No. 62/141,337, filed  
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62/068,526, filed on Oct. 24, 2014, provisional  
application No. 62/068,523, filed on Oct. 24, 2014,  
provisional application No. 62/068,514, filed on Oct.  
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62/068,534, filed on Oct. 24, 2014.(51) **Int. Cl.**  
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**A61K 38/00** (2006.01)(52) **U.S. Cl.**CPC ..... **C07K 14/50** (2013.01); **A61K 38/1825**  
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None

See application file for complete search history.

(56) **References Cited**

## U.S. PATENT DOCUMENTS

|           |   |         |                      |
|-----------|---|---------|----------------------|
| 2,968,158 | A | 1/1961  | Ruschig et al.       |
| 3,097,242 | A | 7/1963  | Hoehn et al.         |
| 3,454,635 | A | 7/1969  | Weber et al.         |
| 3,501,495 | A | 3/1970  | Beregi et al.        |
| 3,654,357 | A | 4/1972  | Bretschneider et al. |
| 3,668,215 | A | 6/1972  | Plumpe et al.        |
| 3,669,966 | A | 6/1972  | Ambrogio et al.      |
| 3,708,486 | A | 1/1973  | Kutter et al.        |
| 3,773,919 | A | 11/1973 | Boswell et al.       |
| 4,287,200 | A | 9/1981  | Kawamatsu et al.     |
| 4,289,872 | A | 9/1981  | Denkewaiter et al.   |
| 4,412,989 | A | 11/1983 | Iwashita et al.      |
| 4,414,148 | A | 11/1983 | Jansen et al.        |
| 4,452,747 | A | 6/1984  | Gersonde             |
| 4,485,045 | A | 11/1984 | Regen                |
| 4,511,502 | A | 4/1985  | Builder et al.       |
| 4,511,503 | A | 4/1985  | Olson et al.         |
| 4,512,922 | A | 4/1985  | Jones et al.         |
| 4,544,545 | A | 10/1985 | Ryan et al.          |
| 4,551,433 | A | 11/1985 | Deboer               |
| 4,569,789 | A | 2/1986  | Blattler et al.      |

(Continued)

## FOREIGN PATENT DOCUMENTS

|    |         |        |
|----|---------|--------|
| AU | 1740283 | 2/1984 |
| CA | 2300362 | 2/1999 |

(Continued)

## OTHER PUBLICATIONS

BMS Press Release "Bristol-Myers Squibb's BMS-986036 (Pegylated  
FGF21) Shows Consistent improvement in Liver Fat, Liver Injury  
and Fibrosis in Patients with Nonalcoholic Steatohepatitis (NASH)  
in Phase 2 Trial" Apr. 2017. 3 pages, [https://news.bms.com/press-  
release/bmy/bristol-myers-squibbs-bms-986036-pegylated-fgf21-  
shows-consistent-improvement-live](https://news.bms.com/press-release/bmy/bristol-myers-squibbs-bms-986036-pegylated-fgf21-shows-consistent-improvement-live).

(Continued)

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Donelson, Bearman, Caldwell & Berkowitz PC(57) **ABSTRACT**Modified FGF-21 polypeptides and uses thereof are pro-  
vided, for example, for the treatment of diseases associated  
with fibrosis. Modified FGF-21 polypeptides are disclosed  
that contain an internal deletion and optionally replacement  
peptide, optionally modified with at least one non-naturally-  
encoded amino acid, and/or optionally fused to a fusion  
partner.**22 Claims, 81 Drawing Sheets****Specification includes a Sequence Listing.**